REMARKS

Amendments

Claims 1 and 5-7 are amended to address matters of formality; Claim 1 is also amended to refer to various elements as "first" or "second", as appropriate; Claims 2 and 4 are amended to make plural "target sites"; Claim 3 is amended to recite that both GFP and RFP are used. Product-limited dependent method claims are similarly amended.

New claims 26-28 are directed to the embodiment of the invention where both markers are fluorescent proteins. The Examiner indicated that claims of this scope are free of the prior art. New claims 29-30 are directed to a method of generating and marking chromosome recombination in somatic cells in a mouse, by crossing the mouse recited in claim 1 with a mouse that expresses a recombinase (e.g. Cre recombinase), to generate progeny mice, etc. (e.g. Specification, paragraph bridging p. 9-10)

The fee for five additional claims is provided with the attached PTO-2038. These amendments do not change the scope or subject matter of the claims and introduce no new matter.

Restriction

Applicants request rejoinder of product-limited dependent method claims.

35USC112, second paragraph

Claim 1 expressly states the functional limitations, and antecedent basis for "the second marker" exists in part (a) of claim 1. Claims 6 and 7 recite structural limitations. Claim 5 avoids the "such as" phrase. Antecedent basis for "the second marker" in claim 5 exists in part (a) of claim 1.

35USC102

Mao et al. (Blood 97(1):324-326, January 2001)describe EGFP reporter mouse strains for monitoring Cre recombinase-mediated excision. In the presence of recombinase a *loxP*-flanked Stop fragment upstream of the EGFP reporter is excised, resulting in EGFP expression. Thus, Mao's EGFP marker is expressed simply by excision of an upstream stop sequence; no interchromosomal recombination is required. There is no teaching or suggestion in Mao of

generating a mouse that has a chromosome pair, with a first chromosome containing a chimeric sequence encoding an **N-terminal portion of a first marker and a C-terminal portion of a second marker separated by a first target site of a recombinase**; and a second chromosome of the pair having at a homologous location a chimeric sequence encoding an **N-terminal portion of the second marker and a C-terminal portion of the first marker separated by a second recombinase target site** as required by the instant claims. Unlike the EGFP reporter of Mao et al, the chimeric sequences recited in parts (a) and (b) of Claim 1 encode only marker portions, wherein recombination between the chromosome pair is required to generate functional markers by recombining the C-terminal portion of each marker with its respective N-terminal portion. No such strategy is contemplated by Mao et al.

Kawamoto et al. (FEBS 470:263-268, 2000) describe EGFP reporter mouse strains for monitoring Cre recombinase-mediated excision. The reporter construct comprises a CAG promoter, a *loxP*-flanked CAT gene, and the EGFP gene. In these reporter mice, the CAT gene is driven by the CAG promoter before recombination, while the EGFP gene is driven by the same CAG promoter only after Cre-mediated recombination. Thus, Kawamoto's EGFP marker is expressed simply by excision of an upstream CAT gene; no interchromosomal recombination is required. There is no teaching or suggestion in Kawamoto of generating a mouse that has a chromosome pair, with a first chromosome containing a chimeric sequence encoding an **N-terminal portion of a first marker and a C-terminal portion of a second marker separated by a first target site of a recombinase**; and a second chromosome of the pair having at a homologous location a chimeric sequence encoding an **N-terminal portion of the second marker and a C-terminal portion of the first marker separated by a second recombinase target site** as required by the instant claims. Unlike the EGFP reporter of Kawamoto et al, the chimeric sequences recited in parts (a) and (b) of Claim 1 encode only marker portions, wherein recombination between the chromosome pair is required to generate functional markers by recombining the C-terminal portion of each marker with its respective N-terminal portion. No such strategy is contemplated by Kawamoto et al.

In short, the cited references do not disclose or suggest anything about a mouse reporter system in which recombinase-mediated interchromosomal recombination is required for

functional expression of a marker. Absent such a prior teaching or suggestion, the claims are in compliance with 35USC102 & 35USC103.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language. Please charge our Deposit Account No. 19-0750 (order S03-250) any fees, necessary extensions of time, or credit any overcharges relating to this communication.

Respectfully submitted,
Science & Technology Law Group

Richard Aron Osman, J.D., Ph.D., Reg. No. 36,627
Tel (949) 218-1757; Fax (949) 218-1767

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